

ATS Highlights 2024: Critical Care Assembly Early Career Professionals



Maria Plataki, MD PhD

Assistant Professor of Medicine

Joan and Sanford I. Weill Department of Medicine

Division of Pulmonary and Critical Care

Weill Cornell Medicine

Email: map2095@med.cornell.edu

Tell us about yourself.

I am a pulmonary critical care physician scientist with a passion for ARDS and acute lung injury pathophysiology. I am also a first-generation immigrant born and raised in Greece. Above all I am the mom of the two cutest boys in the world.

Is your research clinical, basic science, or translational?

I consider my research translational, using mouse models, human specimens and basic science methodology to disentangle and explain clinical observations.

Tell us about your research.

I am investigating how perturbations in lipid metabolism, especially in alveolar type 2 cells, contribute to acute lung injury using high fat diet induced obesity as an extreme paradigm.

Where do you see yourself in 5 years?

Ideally as an intensivist and independently funded researcher bridging the gaps of knowledge regarding the contribution of lipid metabolism in lung health and disease.

How has the Critical Care Assembly contributed to your career?

Through introducing me to peers with similar interests as well as mentors, opening avenues for collaboration, bringing existing supportive mechanisms to my attention. The Critical Care Assembly has also facilitated my participation in the ATS conference through the Travel Award.

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Fatty acid oxidation downregulation in alveolar epithelial type 2 cells promotes obesity associated acute lung injury

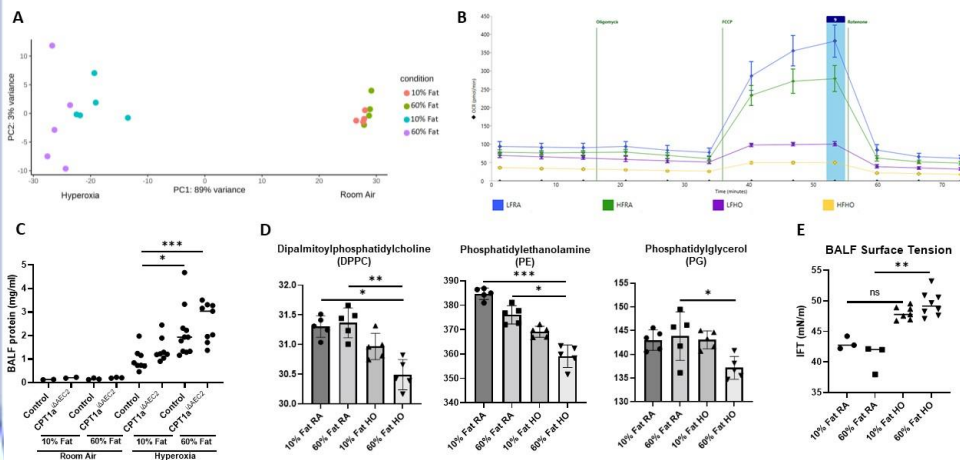
E. Kallinos, Lisa Torres, Divya Bhatia, Baran Ersoy, Heather Stout Delgado, A. Choi, **M. Plataki**

Rationale: Obesity is associated with increased risk for acute respiratory distress syndrome (ARDS). We have shown that mice on a high fat diet incur more lung injury in a hyperoxic model of ARDS and have increased bronchoalveolar lavage fluid (BALF) free fatty acids (FA). Alveolar epithelial type 2 cell (AEC2) function is critical for the pathogenesis of ARDS and lipid metabolism is central to AEC2 to produce surfactant. Mitochondrial FA oxidation (FAO) is a key pathway in lipid breakdown and carnitine palmitoyltransferase 1a (CPT1a) is a rate-limiting enzyme that initiates the uptake of FA by the mitochondria. The aim of this study was to explore the role of FAO in obesity associated acute lung injury.

Methods: C57BL/6 mice received 60% fat versus ingredient matched 10% fat diet for 12 weeks. Mice were exposed to >95% oxygen to induce lung damage. AEC2 were isolated for RNA sequencing, lipidomics, Seahorse, and Western Blot. AEC2 mitochondrial size and reactive oxygen species (mROS) were determined by flow cytometry. *Cpt1a*^{loxp/loxp} Sftpc^{CreERT2}/± tamoxifen-inducible mice were generated with AEC2 specific CPT1a downregulation.

Results: High fat diet was associated with transcriptomic changes in AEC2 only under hyperoxic conditions (Figure 1A). Ingenuity Pathway Analysis of the mitochondrial related functional differentially expressed genes revealed FAO is one of the most significantly downregulated processes in AEC2 with high compared to low fat diet after hyperoxia. In vitro experiments with MLE12 cells displayed increased intracellular lipids after palmitic acid treatment, but even more so after hyperoxia. Even though there were no significant differences between low and high fat diet in mitochondrial size and mROS, high fat diet was associated with more severe mitochondrial bioenergetic failure with reduced maximal respiratory capacity in hyperoxic AEC2 (1B). CPT1a protein expression was significantly increased in AEC2 of high fat diet mice after hyperoxia. Mice with CPT1a downregulation in AEC2 showed a trend for more severe lung injury compared to control mice after a high fat diet (1C). High fat diet was associated with reduced surfactant related phospholipids in hyperoxic AEC2 (1D) and increased BALF surface tension (1E).

Conclusions: High fat diet is associated with increased lung injury, lung free FA, along with mitochondrial and surfactant related lipid alterations in AEC2 in a rodent model of hyperoxic ARDS. FAO in AEC2 may play an important role in the response to acute lung injury in the setting of obesity.



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